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The evolving landscape of HPV-related neoplasia in the head and neck☆,☆☆

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Summary Human papilloma virus (HPV) has emerged as the key etiologic driver in the majority of cancers at head and neck mucosal sites. First described in the uterine cervix and subsequently in oropharyngeal squamous cell carcinomas, the morphologic and clinical spectrum of HPV-related neoplasia has continued to expand and now includes a newly described entity in the sinonasal tract. A recent study has also suggested a role of HPV in some ocular adnexal sebaceous carcinomas. Herein, we review and concisely summarize the spectrum of HPV-driven neoplasia in the head and neck, with a focus on variant morphologies and newly-described entities including key differential diagnoses and clinical implications.

1. Introduction

Human papilloma virus (HPV) has been increasingly recognized as a key etiologic driver in carcinomas of the head and neck [1]. HPV-related oropharyngeal carcinoma (HPV-OPC), the prototypic manifestation of HPV-related neoplasia in this region, is a distinct entity recognized by both the World Health Organization (WHO) and the American Joint Committee on Cancer (AJCC) with specific clinicopathologic features [2,3]. HPV-OPC most often originates in the tonsillar tissue of the tongue base as well as the pharyngeal and palatine tonsils. The typical histologic presentation is "nonkeratinizing squamous cell carcinoma with basaloid morphology" [4,5]. In contrast, conventional (non-HPV-related) squamous cell carcinomas can be located anywhere in the squamous-lined aerodigestive tract, with a preference for the oral cavity. These typically occur in older patients, display keratinizing morphology, and are unrelated to HPV, with tobacco and alcohol as primary risk factors [6]. HPV-OPC may demonstrate early metastasis to cervical lymph nodes, often presenting clinically with a unilateral neck mass. Despite worrisome histologic features and early lymph node metastasis, HPV-OPC often responds well to resection and chemoradiation, and has an overall favorable prognosis compared to keratinizing squamous cell carcinoma [7,8].

Although HPV-OPC with nonkeratinizing squamous morphology is the prototypic HPV-mediated carcinoma in the head and neck, additional variants have been described. These include papillary, spindle cell, neuroendocrine, and

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adenosquamous types [9]. The majority arise in the same anatomic sites as more typical oropharyngeal carcinoma, and the majority display a similar clinical course. However, certain variants such as small cell neuroendocrine types are more clinically aggressive [10-12]. The unusual appearance of these morphologic variants can lead to confusion with other entities. For example, papillary HPV-OPC can be mistaken for metastatic papillary thyroid carcinoma. Correct classification and identification of high-risk HPV (hrHPV) is critical in these cases, to ensure proper patient management.

The clinicopathologic scope of HPV-related neoplasia in the head and neck has recently expanded. In the nasal cavity, HPV-associated multiphenotypic sinonasal carcinoma is a high-grade neoplasm which often presents with a large mass [13-18]. These tumors histologically resemble salivary gland neoplasms with high grade features, but behave in a relatively indolent fashion. Most recently, transcriptionally-active HPV has been identified in a subset of ocular adnexal sebaceous carcinomas, further expanding the histopathologic spectrum of malignancy driven by this oncogenic virus [19].

Herein, we examine unusual and newly-recognized forms of HPV-related neoplasia in the head and neck with emphasis on distinctive histopathologic features, HPV detection, and clinical significance.

2. Oropharynx

The most common site for head and neck HPV-mediated carcinomas is the lymphoepithelium of the tonsillar crypts in the oropharynx. This predilection is poorly understood, but may be due to the unique immunologic function of the tonsillar crypts [5]. Over 90% of HPV-OPC are attributable to HPV16 [20,21]. Additional identified HPV types include 18, 31, 33, and 35. In the oropharynx, immunohistochemistry (IHC) for p16 protein overexpression (Fig. 1B) has been shown to be a reliable, cost effective surrogate for HPV infection when compared to more specific methodologies such as in situ hybridization (ISH) [22]. However, p16 IHC may lack specificity in certain molecular-genetic backgrounds, as will be discussed later in this review. (See Table 1.)

3. Nonkeratinizing squamous

HPV-OPC most often manifests as nonkeratinizing squamous cell carcinoma (SCC). Unlike conventional (non-HPV-

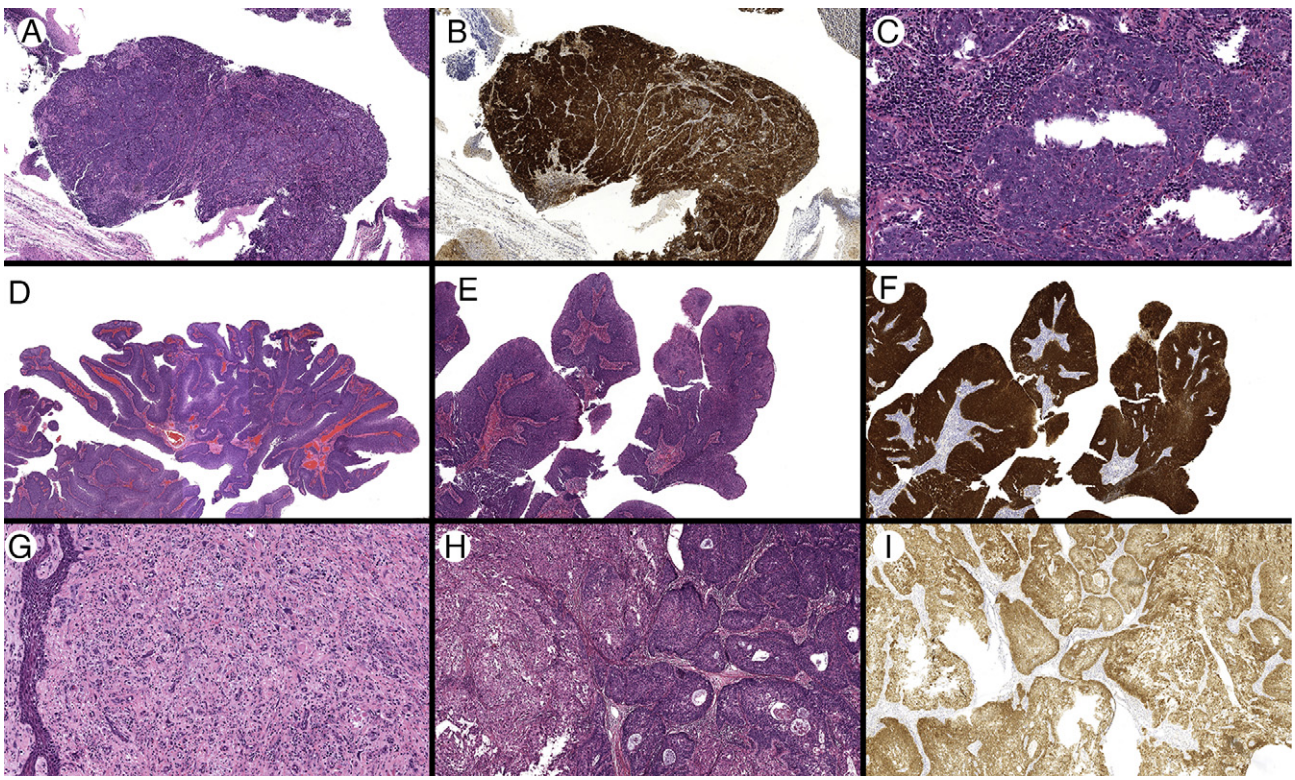

Fig. 1 Variants of HPV-associated oropharyngeal carcinoma. Usual non-keratinizing squamous variant (A) showing strong nuclear and cytoplasmic positivity for p16 by IHC (B). Higher power image showing basaloid cells with scant cytoplasm and nuclear pleomorphism (C). HPV-OPC occasionally displays prominent papillary growth pattern (D-E). p16 IHC demonstrates strong nuclear and cytoplasmic positivity (F). Sarcomatoid carcinoma with scattered pleomorphic spindled cells in a fibrotic background (G). Adenosquamous carcinoma shows separate but closely associated squamous and glandular components (1H). In situ hybridization for high risk HPV is positive in both components (I).

Table 1 Manifestations of HPV-related malignancy in the head and neck

		HPV-related oropharyngeal carcinoma	HPV-related multiphenotypic sinonasal carcinoma	Occular adnexal sebbaceous carcinoma
Clinical Features	Onset	• Median 6th decade of life	• Median 6th decade of life	• Median 6th decade of life
	Prevalance	• One of most common head and neck carcinomas, incidence increasing in U.S.	• Rare	• Rare (5% of primary eyelid tumors) - Small subset recently suggested to harbor hrHPV
	Primary Site	• Primary oropharyngeal tumor may be small and difficult to detect	• Presents as large mass centered in nasal cavity; ± sinus involvement	• Presents as eyelid mass
	Behavior/ Prognosis	• Often presents with neck mass due to cervical lymph node metastasis	• Regional recurrence in 35% of cases. No lymph node metastases	• No local recurrence in few HPV+ cases identified
		• Usually respond well to chemoradiation	• Rare distant metastasis, usually to lung	• One HPV+ case had distant and lymph node metastasis
		• Favorable prognosis compared to non-HPV-related carcinomas of the oropharynx and oral cavity (Overall 3 year survival 82% for HPV versus 57% for non-HPV)	• Favorable overall prognosis compared to non-HPV-related carcinomas of the sinonasal tract	• Further study required to characterize HPV-positive subset. Suggestion of improved prognosis in limited reported cases.
Pathologic Features	Morphology	• Non-keratinizing squamous most common (See Table 2 for other variants)	• Myoepithelial, ductal, and squamoid components	• Clear cells abundant in well-differentiated cases, may be only focal in high grade cases
		• Basaloid appearance with high N:C ratio, indistinct cell borders, hyperchromatic nuclei with indistinct nucleoli	• Sheets, nest, and cribriform growth of basaloid cells	• Dermal-based tumor with nodular or solid growth pattern. Frequent basaloid or squamoid cytologic features may lead to misdiagnosis
		• Mitoses, apoptoses, and necrosis often present	• Mitoses and necrosis seen in 1/3 of cases, rare sarcomatoid differentiation or heterologous elements	• Mitoses and necrosis in high-grade cases
		• No terminology for squamous dysplasia in oropharynx - carcinoma in situ is classified as HPV-OPC as it may be associated with lymph node metastasis in the absence of clear invasion	• Overlying squamous dysplasia may be seen in surface epithelium	• No association with squamous dysplasia. May show focal connection to overlying epidermis with or without pagetoid spread
	IHC	• p16 diffusely positive	• p16 diffusely positive	• p16 diffusely positive
		• Squamous markers typically positive (CK5/6, p40, p63)	• Myoepithelial markers positive (S100, calponin, SMA, p40)	• Adipophilin, androgen receptor, factor XIIIA, EMA positive
	hrHPV	• p16 positivity is adequate surrogate for hrHPV testing	• hrHPV positivity should be confirmed with ISH	• hrHPV positivity should be confirmed with ISH
		• HPV type 16 most common (>90% of cases)	• HPV type 33 most common	• hrHPV found in small subset of cases. Further study required to confirm association

related) squamous cell carcinoma, a visible dysplasia to carcinoma progression does not occur in HPV-OPC [9]. Even cases of carcinoma in situ (CIS) without a clearly identifiable invasive component can present with locally metastatic disease [23]. This is likely due to the anatomic structure of the tonsillar crypts with ample access to lymphatics. For this reason, in situ lesions are no longer recognized in the current AJCC staging protocol [3]. All HPV-SCC are considered invasive with the potential for metastasis.

3.1. Key histologic features

- HPV-OPC resembles the reticulated tonsillar epithelium from which it is derived [9,24] (Fig. 1A).
- Tumor cells have indistinct cell borders, high nuclear to cytoplasmic ratio, and round to oval, hyperchromatic nuclei with inconspicuous nucleoli [25] (Fig. 1C). (See Tables 3 and 4B.)

Table 2 Morphologic variants of HPV-related oropharyngeal carcinoma

Squamous (non-keratinizing)
Adenosquamous
Adenocarcinoma
Sarcomatoid
Neuroendocrine
Papillary
Lymphoepithelial-like

Table 3 Differentiating features of mucoepidermoid carcinoma versus HPV-related adenosquamous carcinoma

Mucoepidermoid carcinoma	HPV-adenosquamous
• Composed of mucinous, epidermoid, and intermediate cells	• Contains malignant squamous and glandular components
• Components are often intimately admixed	• Components are typically regionally distributed rather than intimately admixed throughout tumor
• Scattered or nested mucocytes present (can highlight with mucicarmine)	• Glandular areas may have intra- and extra-cellular mucin (not required for diagnosis)
• Squamoid cells forming nests or scattered throughout, true keratinization is rare	• Squamous areas appear similar to HPV-SCC, often with basaloid appearance
• p16 may be positive, especially if high grade	• Strong and diffuse p16 in both components
• HPV negative by ISH	• HPV detectable in both glandular and squamous areas
• Detectable *MAML2* translocations in up to 70% of tumors	• No *MAML2* translocation

- When present, invasion often takes on a nested or solid nodular architecture, often with an associated lymphocyte-predominant inflammatory infiltrate.
- The desmoplastic stromal response characteristic of conventional SCC is rarely seen. As previously mentioned, most cases are predominantly nonkeratinizing and convey a blue, basaloid appearance at low power. However, focal areas of maturation and keratinization can be seen. Mitoses and apoptotic bodies are prominent, and areas of necrosis may be present [4,5,9,24,25].

3.2. Cervical metastasis

- When metastasizing to cervical lymph nodes, HPV-OPC often forms a cystic neck mass which may radiologically and pathologically resemble a benign branchial cleft cyst [5]. This can be particularly challenging, as it may be the initial presentation of HPV-OPC. In these situations, thorough histologic sampling, HPV testing, and clinical investigation for an ipsilateral primary tumor in the oropharynx can be helpful [9].
- Fine needle aspiration is also often utilized in the diagnosis of cervical metastasis. The identification of nuclear pleomorphism is highly specific in differentiating cystic metastatic SCC from branchial cleft cyst in this setting [26]. Other features of malignancy include high nuclear/cytoplasmic ratio, irregular nuclear membranes, and necrosis. However, carcinoma cannot be completely excluded in cystic lesions which lack overt cytologic features of malignancy [26,27]. HPV detection by ISH can be helpful in these cases [9,26].
- p16 positivity alone is insufficient to diagnose carcinoma in these cases, as nearly 50% of benign branchial cleft cysts may be found to show p16 overexpression [28].
- In some cases of HPV-related carcinoma metastatic to cervical lymph node(s), a primary tumor is never identified in the oropharynx despite thorough clinical workup and histologic sampling. This may be due to regression of the

Table 4 Differentiating features of cystic neck mass

Cystic metastatic HPV-SCC	Metastatic ciliated adenosquamous	Branchial cleft cyst
• Typically adults (median 6th decade of life)	• Typically children, but may rarely enlarge during adulthood especially following infection	• Typically children, but may rarely enlarge during adulthood especially following infection
• May form relatively bland-appearing squamous-lined cystic mass	• May form cystic spaces lined by bland-appearing glandular cells with at least focal cilia	• Cysts lined by bland columnar or metaplastic squamous epithelium
• However, most cases display atypical squamous cells with irregular nuclear membranes, high nuclear:cytoplasmic ratio, and variable pleomorphism	• Often display other areas with high grade glandular and squamous components	• Lack of cytologic atypia
• ± keratinization	• Squamous areas ± keratinization	• Squamous-lined cysts may be filled with keratinaceous debris
• Residual lymph node architecture may be partially or completely obliterated	• Residual lymph node architecture may be partially or completely obliterated	• Cysts often associated with lymphoid tissue which may simulate a lymph node
• Diffuse nuclear and cytoplasmic p16 staining	• Diffuse nuclear and cytoplasmic p16 staining	• Up to 50% may be focally p16 positive
• HR-HPV detectable by ISH	• HR-HPV detectable by ISH	• HR-HPV negative

primary tumor or, more likely, a microscopic primary tumor which cannot be located [24].

3.3. Basaloid morphology

- Most HPV-OPC display a variable basaloid cytomorphology, typically consisting of a conventional squamous cell carcinoma with an adjacent basaloid component showing solid and nested growth of angulated cells with scant cytoplasm, nuclear hyperchromasia, and nuclear palisading [29-31].
- The tumor nests often mold together in a "jigsaw" pattern [31]. HPV-OPC demonstrating this histologic pattern behaves in similar fashion to other HPV-OPC [29,30].
- In some cases, however, the basaloid morphology predominates, and such tumors resemble the basaloid variant of conventional squamous cell carcinoma seen elsewhere in the upper aerodigestive tract [29-32].
- Moreover, p16 IHC or HPV testing is important in these tumors, as non-HPV-related basaloid carcinomas are clinically aggressive and convey a poor prognosis [31,32].

4. Adenosquamous and "ciliated adenosquamous"

- HPV-related carcinomas of both the oropharynx and sinonasal tract may occasionally exhibit biphasic squamous and glandular differentiation [33-35](Fig. 1H).
- The adenocarcinomatous component often exhibits a high-grade cytomorphology with ducts or papillae lined by cuboidal to columnar cells which may appear single-layered or pseudostratified [9,33,34].
- Mucin production may also be identified, although this is not required for diagnosis [33].
- Adenocarcinomatous areas often display high grade features including nuclear pleomorphism, mitoses, apoptoses, and necrosis.
- The squamous component appears similar to that previously described for HPV-SCC.
- High-risk HPV can be detected in both the squamous and glandular components using in-situ hybridization, and both components demonstrate p16 positivity [33-35].
- In contrast to non-HPV-mediated adenosquamous carcinomas of the larynx and oral cavity, HPV-related carcinomas with this morphology typically respond favorably to chemoradiation with a similar prognosis to the pure squamous variant of HPV-OPC. It is therefore critical to differentiate these entities by the presence of transcriptionally active HPV [33-35] (Fig. 1I).

4.1. Ciliated adenosquamous

- In rare cases, the glandular component may appear remarkably low grade. These tumors display glandular and cystic spaces lined by bland single-layered cuboidal to columnar cells. Cilia may even be visible in some cases, which is traditionally considered a feature of benignity (Fig. 2A). These tumors have been termed "ciliated adenosquamous carcinomas" and may pose diagnostic difficulty for pathologists if inadequately sampled [36-40].
- In cases with solitary lymph node metastasis for example, the tumor may form cystic spaces lined by bland ciliated cells resembling a benign branchial cleft cyst. However, high grade squamous and glandular elements are usually visible in other areas [40] (Fig. 2B).
- p16 IHC alone is insufficient to diagnose carcinoma in this setting (Fig. 2C), as branchial cleft cysts may also stain

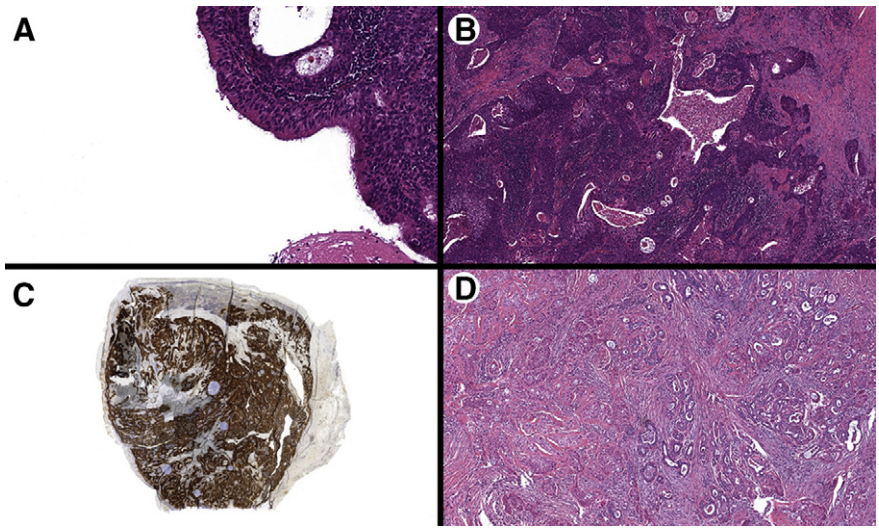

Fig. 2 Ciliated adenosquamous carcinoma metastatic to cervical lymph node. Focal areas demonstrate cyst formation with bland-appearing glandular cells and ciliated apical surface (A). Other areas show high grade squamous and glandular elements (B). p16 IHC is strongly positive in both components (C). In contrast, mucoepidermoid carcinoma demonstrates intimately admixed squamoid and glandular elements (D).

positive [28]. Confirmation of HPV positivity by ISH can be used in difficult cases.

4.2. Cervical metastasis

- Similar to HPV-related squamous carcinoma, cervical metastasis may be the initial presentation for a subset of patients. Typically, an oropharyngeal tumor with similar biphasic morphology is later identified. However, in some cases a primary tumor is never located [40].
- An important differential diagnostic consideration for cervical metastasis is mucoepidermoid carcinoma. However, the squamoid and glandular components of mucoepidermoid carcinoma are intimately intermingled in most cases (Fig. 2D), rather than forming separate but closely associated tumor components [33]. Identification of mucin production is required for mucoepidermoid carcinoma, but not for adenosquamous carcinoma. The definitive distinguishing feature is the demonstration of hrHPV by ISH, which excludes mucoepidermoid carcinoma. Again, p16 is insufficient to distinguish these entities, as it may be up-regulated in a subset of mucoepidermoid carcinoma [39,40].
- In addition, FISH for MAML2 can be helpful when positive as it is quite specific for mucoepidermoid carcinoma [33].

5. Adenocarcinoma

- In rare cases, carcinomas arising in the oropharynx show a pure glandular morphology with a similar appearance to the glandular element in adenosquamous carcinomas [41-43].
- Only four cases have been reported to date, with at least one patient dying of disease [41-43].
- Differential diagnostic considerations include salivary gland carcinoma and metastatic carcinoma, both of which may be excluded by paired p16 IHC and direct testing for hrHPV by ISH or PCR [41-43].

6. Sarcomatoid carcinoma

- Sarcomatoid carcinoma, also called spindle cell carcinoma, refers to malignant epithelial neoplasms exhibiting a component of mesenchymal differentiation [44,45].
- These lesions most commonly arise as an exophytic mass in the oral cavity or larynx and are unrelated to HPV. However, rare cases of sarcomatoid carcinoma have been shown to harbor transcriptionally active HPV [44,45].
- The majority of HPV-related cases have been reported in the oropharynx [44]. However, rare laryngeal cases have been reported despite the relative infrequency of HPV-related carcinoma in this anatomic site [45].
- Sarcomatoid areas consist of sheets of spindled or pleomorphic cells. Some cases may show markedly atypical pleomorphic cells in a background of fibrosis (Fig. 1G). In roughly half of cases, an associated squamous cell component or squamous carcinoma in situ can be identified [46].
- In cases without morphologic evidence of squamous differentiation, a broad immunohistochemical panel for keratins and p63/p40 should be applied. However, it should be noted that sarcomatoid carcinomas often show down-regulation of keratin expression [46].
- In HPV-related cases, the identification of HPV alone may be sufficient evidence of squamous origin due to the epitheliotrophism of the virus [33]. The pathologist should maintain a high degree of suspicion for sarcomatoid carcinoma when encountering a spindle cell lesion in the upper aerodigestive tract due to the relative frequency of carcinoma compared to primary sarcomas in this region.
- Although the overall number of reported HPV-related sarcomatoid carcinomas is limited, some authors have suggested a favorable prognosis compared to non HPV-related cases [45]. Therefore, the identification of hrHPV via p16 IHC and/or ISH may provide helpful prognostic information, and testing should be at least considered for all cases – particularly those occurring in the oropharynx.

7. Neuroendocrine carcinoma

Neuroendocrine carcinomas have been known to rarely occur in the upper aerodigestive tract, and a subset of these tumors has been shown to harbor hrHPV [10-12,47-49]. HPV-related cases have been reported in the oropharynx and sinonasal tract.

- The majority of cases have resembled small cell neuroendocrine carcinoma of other sites with high nuclear to cytoplasmic ratio, hyperchromatic nuclei without nucleoli, nuclear molding, high mitotic rate, and frequent apoptoses [10-12,47,48].
- Adjacent nonkeratinizing squamous cell carcinoma or carcinoma in situ can occasionally be seen [10-12,48].
- In some cases, neuroendocrine features may be difficult to distinguish from high-grade areas in nonkeratinizing squamous HPV-OPC. In such cases, immunohistochemical expression of one or more neuroendocrine markers (synaptophysin, chromogranin, and CD56) can be helpful. In addition, CK5/6 and p63 expression are typically absent in reported cases of HPV-related neuroendocrine carcinoma [12,47]. However, p40 expression was not examined in most cases.
- The main differential diagnostic consideration is metastatic neuroendocrine carcinoma from another site. TTF-1 shows variable staining in primary head and neck small cell carcinoma, and is not a reliable marker to distinguish from metastatic small cell lung carcinoma [12].
- The identification of hrHPV or visualization of adjacent non-small cell carcinoma can confirm a primary head and neck tumor.
- Immunohistochemical overexpression of p16 is frequently seen in small cell carcinoma of other sites, and is an

insufficient surrogate for HPV testing in this situation. Further, rare typical and atypical carcinoid tumors have been reported in the upper aerodigestive tract [49,50]. These tumors can be excluded using histologic criteria for high grade neuroendocrine tumors including mitotic count and presence of necrosis [47,49,50].

- Unlike other HPV-related head and neck tumors, neuroendocrine carcinomas typically exhibit aggressive behavior with early metastasis and poor overall survival [10-12,48]. However, a small number of patients have demonstrated long-term survival which may suggest a marginally better prognosis compared to non-HPV-related neuroendocrine carcinomas [11,12]. One patient showed initial response to a chemoradiation protocol frequently used in small cell lung carcinoma [47]. However, the follow-up interval was relatively short.

7.1. Large cell neuroendocrine

- Rare cases of HPV-related large cell neuroendocrine carcinoma arising in the oropharynx and sinonasal tract have also been identified and appear to behave in a similarly aggressive fashion [51].
- Morphologically, these tumors demonstrate trabecular or solid/nested growth pattern and often demonstrate rosettes, peripheral palisading, and/or organoid nests.
- Tumor cells appear large and polygonal with prominent nucleoli, numerous mitoses, and frequent necrosis. Most cases do not demonstrate an adjacent squamous component.
- Neuroendocrine differentiation can be identified with immunohistochemistry for synaptophysin, chromogranin, and CD56. In a recent series of three cases, all patients presented with metastatic or locally advanced disease, and two died of their disease within a year [51].

8. Papillary

HPV-OPC may occasionally demonstrate exophytic papillary growth with true fibrovascular cores lined by nonkeratinizing squamous epithelium [52,53](Fig. 1D-F). These cases typically demonstrate a favorable prognosis, similar to HPV-related squamous carcinomas. The significance of the papillary growth pattern is principally recognition that these may be HPV related tumors and to avoid confusion with other tumor types with papillary growth such as metastatic papillary thyroid carcinoma.

9. Lymphoepithelial-like (undifferentiated)

The lymphoepithelial-like variant of HPV-OPC carcinoma closely resembles nasopharyngeal carcinoma with solid nests, trabeculae, and single cell growth of epithelial cells surrounded by abundant lymphocytes and plasma cells [54,55]. Historically, these tumors have been referred to by a variety of names including "nasopharyngeal-like" and "nonkeratinizing undifferentiated" carcinoma. In contrast to nasopharyngeal carcinoma, which is associated with Epstein–Barr virus, lymphoepithelial-like carcinomas of the oropharynx typically demonstrate transcriptionally active HPV [54,55]. These tumors show a favorable prognosis similar to HPV-related squamous carcinoma. Importantly, rare cases of HPV-related lymphoepithelial-like carcinomas have been identified in the sinonasal tract [35]. Therefore, anatomic site alone is insufficient to distinguish these tumors, which can be confirmed with ISH for EBV and HPV [54,55].

10. Oral cavity, hypopharynx, and larynx

While HPV-related oropharyngeal carcinoma has been well-characterized, the role of hrHPV in head and neck carcinomas arising in other anatomic sites is less clear. In these locations, reports of HPV positivity vary widely depending on the detection methods utilized [56]. Studies utilizing viral PCR report high levels of positivity in malignant and premalignant lesions. However, strict methodology including a combination of ISH, p16 IHC, and viral E6 qPCR resulted in only 4% HPV positivity in squamous carcinomas arising in the oral cavity, hypopharynx, and larynx [57]. Non-keratinizing squamous histology remains most common in these extra-tonsillar sites, but other histologic variants may occur.

11. Nasopharynx

Transcriptionally-active HPV can be detected in approximately 20% of carcinomas arising in the nasopharynx [35]. Of these, most are non-keratinizing squamous cell carcinomas with approximately 30% of sinonasal squamous carcinomas being attributable to hrHPV. Other histologic types such as small cell neuroendocrine carcinoma and lymphoepithelial-like carcinoma have also been identified in this anatomic site.

11.1. HPV-related multiphenotypic sinonasal carcinoma (HRMSC)

HRMSC is a distinct clinicopathologic entity arising exclusively in the sinonasal tract. This rare neoplasm was first described by Bishop and colleagues under the term "HPV-related carcinoma with adenoid cystic carcinoma-like features" [14]. The name was subsequently updated to HRMSC to adequately reflect the morphologic diversity of this tumor type [15].

- HRMSC typically presents as a large mass centered in the nasal cavity causing epistaxis, nasal obstruction, and headaches/sinus pain [13-18]. The paranasal, ethmoid, sphenoid, and frontal sinuses may also be involved.
- These tumors are histologically characterized by multiple patterns of differentiation including myoepithelial, ductal, and squamoid.

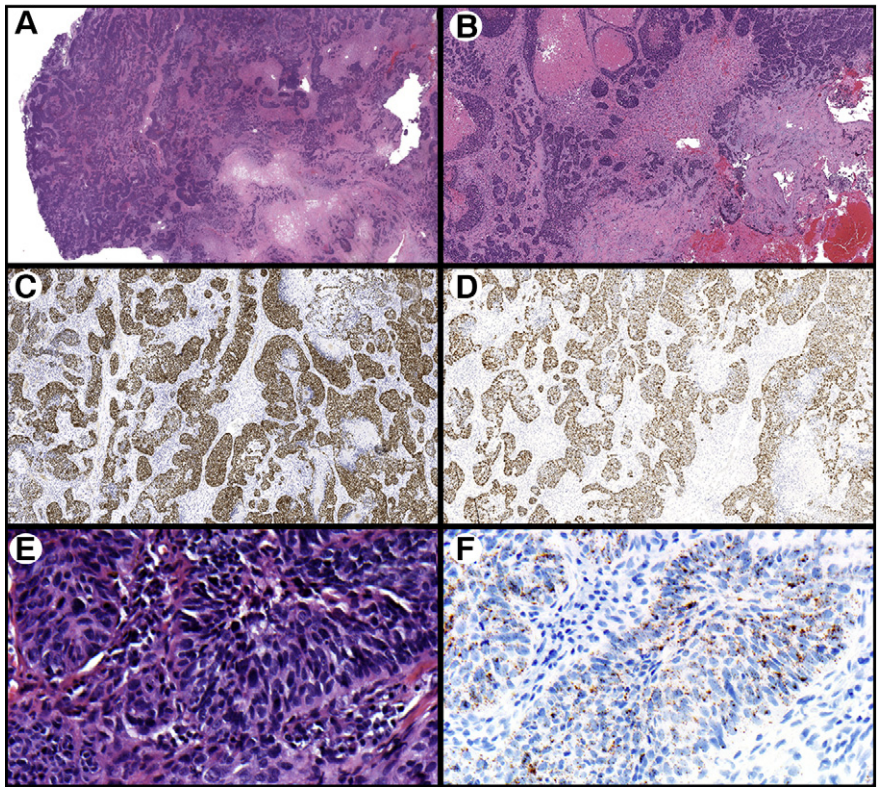

Fig. 3 HPV-related neoplasia outside the oropharynx. HPV-related multiphenotypic sinonasal carcinoma demonstrates solid nests of basaloid cells with focal necrosis, mimicking high grade salivary gland neoplasms (A-B). SOX10 IHC shows strong nuclear positivity (C). In situ hybridization for high risk HPV is positive (D). HPV-related ocular adnexal sebaceous carcinoma (E) with positive in situ hybridization for high risk HPV (F).

- Solid sheets and nests of basaloid cells predominate, and are often separated by thin fibrous septae. Cribriform growth is also frequently seen, which may lead to confusion with high grade adenoid cystic carcinoma (Figs. 3A-3B).
- Focal true duct formation can also be seen.
- Often, adjacent areas of surface epithelial atypia can be identified in the form of conventional squamous dysplasia or as scattered markedly atypical cells within the sinonasal epithelium [14-17].
- Focal squamous differentiation including abrupt keratinization or scattered squamoid rests are seen in a minority of cases.
- The basaloid cells may display cytoplasmic clearing, plasmacytoid appearance, and focal spindling suggestive of myoepithelial differentiation, which can be confirmed with immunohistochemistry for S100, calponin, SMA, and p40. SOX10 is also typically positive, as in many salivary gland neoplasms (Fig. 3C).
- An additional minor component of eosinophilic epithelioid cells is often found admixed with the more frequent basaloid cells.
- High grade features including necrosis and high mitotic rate are seen in roughly 1/3 of cases. Scattered anaplastic cells, sarcomatoid differentiation, and chrondroid/osteoid elements may be seen in rare cases. In cases with the above histologic features, the diagnosis can be confirmed with the detection of hrHPV via specific methods such as ISH (Fig. 3D).
- Immunohistochemical positivity for p16 lacks specificity for this diagnosis, as p16 can be seen in other tumors exhibiting similar morphology, including adenoid cystic carcinoma [14].
- Interestingly, HPV 33 is the most common type identified in HRMSC [14,17]. This contrasts with HPV-OPC as well as HPV-positive squamous carcinomas of the nasopharynx, where HPV 16 is the most common type identified [6,35].
- In keeping with other HPV-related carcinomas of the head and neck, HRMSC is associated with a favorable prognosis despite frequently presenting at advanced local stage. In the largest case series to date, no patients died of disease despite regional recurrences in ~35% of cases [15]. Rare distant metastases have occurred, most frequently to the lungs, but no regional lymph node metastases have been reported. Overall, the prognosis is favorable compared to other high grade neoplasms of the sinonasal tract.

12. Other head and neck sites

12.1. Salivary gland tumors

In the past, a few small studies have reported detecting hrHPV in various primary salivary gland tumors [13,56,58]. However, several recent studies using strict controls have failed to reproduce these results [60-62].

- In one study, HPV was detected in two cases of "adenoid cystic carcinoma" arising in the nasopharynx, but these likely represented HRMSC [13]. In other studies, HPV PCR was combined with p16 IHC to establish the link with hrHPV [58,59]. However, as previously noted, p16 is not a reliable surrogate of HPV transcriptional activity outside the oropharynx, and may be overexpressed in a variety of salivary gland tumors unrelated to HPV [60-62].
- More specific methods such as ISH or E6 PCR with adequate controls would be required to establish a definitive link with transcriptionally-active virus.
- Currently, there is no definitive evidence for a role of hrHPV in the pathogenesis of most primary salivary gland tumors. However, squamous carcinomas arising in the salivary gland may be HPV-associated [61].

12.2. Ocular adnexal sebaceous carcinoma

Ocular adnexal sebaceous carcinoma is a rare, locally aggressive neoplasm that accounts for ~5% of malignant epithelial tumors of the eyelid [63-65].

- Occasional studies over the past have interrogated ocular adnexal sebaceous carcinomas for a relationship to HPV infection, but these results were inconsistent as some groups confirmed HPV infection in a subset of tumors while others did not [66,67].
- In a recent study, Tetzlaff et al defined two distinct molecular subgroups of ocular adnexal sebaceous carcinoma: 1) tumors characterized by *TP53* and *RB1* mutations, and 2) tumors lacking mutations affecting *TP53* or *RB1*—a subset of which harbored transcriptionally active hrHPV [19]. Specifically, next generation sequencing of ocular adnexal sebaceous carcinomas revealed *TP53* and *RB1* mutations in 20/29 patients. These mutations frequently co-existed in the same tumor (14/29 patients). Among the *TP53* and *RB1* wild-type tumors, 4/9 harbored transcriptionally active hrHPV by RNA sequencing and/or in situ hybridization (Figs. 3E-3F). These subgroups appeared to be mutually exclusive, as transcriptionally active HPV was not detected in any of the *TP53/RB1* mutant tumors. Interestingly, the HPV-positive cases occurred in patients significantly younger than those with *TP53/RB1* mutations (54 versus 70.3 years at diagnosis). In addition, whereas all of the locally recurrent tumors in their series harbored *TP53/RB1* mutations compared to the *TP53/RB1* wild type lesions (including the HPV-positive tumors) which did not exhibit local recurrence in their series. If representative, this would suggest a favorable prognostic significance, as seen in other HPV-related tumors. However, this study was limited by relatively few cases, and corroboration of these findings in subsequent studies may be necessary to draw definitive conclusions. If confirmed, HPV-related ocular adnexal sebaceous carcinoma would present a unique histologic manifestation of HPV-related neoplasia in the head and neck, arising in a mucosal site outside of the aerodigestive tract.

13. Summary

- The clinicopathologic spectrum of HPV-related neoplasia continues to expand in the head and neck, conveying implications for treatment, prognosis, and our developing understanding of HPV-mediated carcinogenesis.
- The most common site for HPV-related carcinoma is the oropharynx, which is the only head and neck site where p16 IHC can be considered an adequate surrogate for HPV status of squamous carcinomas.
- Significant morphologic heterogeneity can be seen in HPV-OPC, and the pathologist should be aware of the numerous histologic subtypes that can be seen.
- More specific methods of HPV detection such as ISH should be considered for unusual morphologic types as well as tumors occurring outside the oropharynx. Although extrapharyngeal HPV-related carcinomas are relatively rare, continued investigation has identified HPV in distinct clinicopathologic entities in the sinonasal tract and ocular adnexa.
- These newly-described entities are important to recognize, as prognosis and treatment may differ from non-HPV-related histologic mimics.

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